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USSN: 09/844,501
Dkt. No.: 8325-0015
S15-US1
PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

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2/2/06 Michelle Hobson
Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: Jeffrey N. Fredman
WOLFFE et al.	Group Art Unit: 1637
Serial No.: 09/844,501	Confirmation No.: 9055
Filing Date: April 27, 2001	Customer No.: 20855
Title: DATABASES OF REGULATORY SEQUENCES; METHODS OF MAKING AND USING SAME	

TRANSMITTAL LETTER

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

x Reply Brief (12 pages) with attached Claims Appendix (5 pages)

x Return receipt postcard

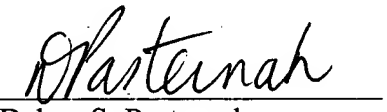
The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	30	- 122	0	x $50.00	$0
Independent Claims	2	- 22	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Petition for Extension of Time					$0
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: February 2, 2006

By: 

Dahna S. Pasternak
Registration No. 41,411

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel.: (650) 493-3400
Fax: (650) 493-3440

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In re application of:

A.P. Wolffe *et al.*

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REPLY BRIEF

ROBINS & PASTERNAK LLP
1731 Embarcadero Road
Suite 230
Palo Alto, CA 94303

Attorney for Appellant

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REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

Pursuant to Section 41.37(c) (69 Fed. Reg. 49962, Aug 2004), Applicants submit the following Reply Brief in Response to the Examiner's Answer mailed on December 5, 2005. A Reply Brief submitted within two months of the date of mailing of the Examiner's Answer, namely by February 5, 2006, is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

STATUS OF THE CLAIMS

Claims 123-152 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on April 27, 2001 with claims 1 to 122. Claims 1 to 122 were canceled and claims 123-152 were newly presented in a second preliminary amendment mailed July 23, 2002 and were variously amended in papers mailed December 17, 2003 and February 26, 2004. Following a telephone conference with the Examiner, Applicants amended the claims in a Supplemental Amendment mailed June 16, 2004, to make explicit what was previously implicit. These amendments were not entered. Accordingly, claims 123-152 are pending as shown in the Claims Appendix. All pending claims remain rejected under 35 U.S.C. § 103.

GROUNDS OF REJECTION

1. Claims 123-152 stand rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,635,355 (hereinafter "Grosveld"), either alone or in combination with the NEB Catalog, U.S. Patent No. 5,500,356 or U.S. Patent No. 6,444,421.

ARGUMENTS

1. A *Prima facie* Case of Obviousness Has Not been Established

The Examiner's Answer maintained the rejection of all examined claims as allegedly obvious over Grosveld (U.S. Patent No. 5,635,355). In support of the rejection, the Examiner asserts that all of the method steps of the claim are taught by Grosveld.[1]

However, in making this rejection, the Examiner combined three different sections of Grosveld (including the claims) to allegedly reconstruct the invention.[2] Despite Appellants' previous requests, no motivation for selecting just those three particular portions of Grosveld's

[1] Examiner's Answer dated December 5, 2005 at pages 9-10

[2] See, for example, Office Action of September 29, 2003 at pages 3-4 and Examiner's Answer dated December 5, 2005 at pages 3-4

disclosure was provided by the Examiner; nor was any motivation provided for the order in which those three particular sections were combined.[3] For these reasons alone, the rejection is improper, inasmuch as the Federal Circuit has stated:

> However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. [ ] Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. [*citations omitted*] Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference.[4]

In this regard, the Examiner misrepresents Appellants' position when he states that ". . . the Appellant does not dispute that Grosveld teaches the steps as illustrated."[5] To the contrary, Appellants have repeatedly argued that Grosveld fails to teach the invention as claimed.[6,7]

The Examiner presented a number of arguments to support his *prima facie* case of obviousness. Appellants address each of these arguments in turn, showing that they are factually and legally deficient and that, therefore, there is no *prima facie* case.

(a) The Term "Library" Has Been Given a Broader Interpretation than Reasonable by the Examiner

The Examiner asserts that Appellants expressly defined the term "library" in the specification and that this "definition" does not require that a library contain different members,[8] relying on *Philips v. AWH*.[9]

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[3] See Appellants' Response dated February 26, 2004 at pages 7-8

[4] *In re Kotzab*, 55 USPQ2d 1313, 1316-1317 (Fed. Cir. 2000)

[5] Examiner's Answer dated December 5, 2005 at page 10

[6] See, for example, Response dated February 26, 2004 at pages 7-8; Response dated May 18, 2004 at page 3; and Appeal Brief dated August 25, 2005 at page 15

[7] See also the section entitled "Limitations from the Preamble . . .," below

The Examiner's position appears to be that a single sentence from the specification[10] has served to redefine and broaden the art-recognized term "library" to the point that it encompasses collections of identical DNA molecules (which are normally referred to by the art-recognized term "clone"). The Examiner also states the claims must be given their broadest reasonable construction, again relying on *Philips*, and that that "the broadest reasonable construction of the term 'library' does not require that the elements differ."[11] However, no evidence is provided to support the Examiner's assertion that the broadest reasonable construction of the term "library" does not require that the elements differ.

In response, Appellants note that, not only *Philips*, but a host of prior case law clearly state that the primary determinant of the meaning of a claim term is the ordinary and customary meaning of that term, and that

> the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.[12]

Nothing in the specification contradicts what one of ordinary skill in the art of molecular biology, as of April 2001, would consider to be the ordinary and customary meaning of the term "library." At that time, the term was known, in the field of molecular biology, to refer to a collection of clones containing different inserts, as evidenced by the use of such terms as "genomic library" and "cDNA library." Appellants have previously provided evidence that the

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[8] Examiner's Answer dated December 5, 2005 at pages 10-11

[9] 75 USPQ2d 1321 (Fed. Cir. 2005)

[10] page 46, lines 6-7

[11] Examiner's Answer dated December 5, 2005 at page 11

[12] *Philips v. AWH*, 75 USPQ2d, 1321, 1326 (Fed. Cir. 2005); see also *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996); *Ferguson Beauregard/Logic Controls v. Mega Sys., LLC*, 350 F.3d 1327, 1338 (Fed. Cir. 2003); *Innova Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004) and *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004)

ordinary and customary meaning of the term "library" did, in fact, require that the elements of the library differ from one another.[13]

Appellants have also pointed out that the passage of the specification cited by the Examiner is not inconsistent with the ordinary and customary meaning of the term "library" and have repeatedly pointed to additional portions of the specification that are consistent with the ordinary and customary meaning of the term,[14] thereby rebutting the assertion that Appellants somehow attempted to redefine the term "library."

As noted above, the Examiner has provided no evidence to support the assertion that the broadest reasonable construction of the term "library" includes collections of identical sequences. In this context, it is informative to review the original rejection, in which the Examiner asserted that

> the term "library" is broadly interpreted as including any collection of nucleic acids, since any collection of nucleic acids can comprise a nucleic acid library.[15]

This statement is nothing but a tautology, since it asserts that, because any collection of nucleic acids can comprise a library, a library is any collection of nucleic acids. It thus has no definitional value. Moreover, no evidence was provided by the Examiner to support his assertion that any collection of nucleic acids can comprise a library. In this regard, MPEP § 2144.03 states that

> Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known.
>
> It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted

[13] See, for example, Response dated May 18, 2004 at pages 2-3 and Exhibits A and B which accompanied that response; see also Appeal Brief dated August 25, 2005 at pages 12-14 and Evidence Appendices 1 and 2 of the Appeal Brief

[14] See Response dated May 18, 2004 at pages 3-4 and Appeal Brief dated August 25, 2005 at page 10

[15] Office Action dated September 29, 2003 at page 2

> to be well-known are not capable of instant and unquestionable demonstration as being well-known. (emphasis in original)
>
> It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697

MPEP § 2144.03 goes on to state that if official notice is taken of a fact, unsupported by documentary evidence, the technical line of reasoning underlying a decision to take such notice must be clear and unmistakable and, further, that if Applicant challenges a factual assertion as not properly officially noticed or not properly based upon common knowledge, the Examiner must support the finding with adequate evidence.

In the present case, no documentary evidence has been provided by the Examiner to support his assertion that a library is any collection of nucleic acids, nor has the examiner provided a technical line of reasoning underlying his decision to assert that a library is any collection of nucleic acids. Appellants, however, have challenged the Examiner's assertion that a library is any collection of nucleic acids, and have provided evidence to support their position.[16]

Thus, the record shows that the official notice taken by the Examiner of the definition of the term "library" is both improper (according to MPEP § 2144.03) and incorrect.[17]

(b) Intrinsic Evidence is Not the Primary Source for Determining the Meaning of a Claim Term and, in the Case on Appeal, Intrinsic Evidence is Entirely Consistent with the Customary Meaning

The Examiner cited *C.R. Bard, Inc. v. U.S. Surgical Corp.*, Fed. Cir 04-1135 to support the proposition that the intrinsic record is the primary source for determining claim meaning, and

[16] See, for example, Response dated May 18, 2004 at pages 2-3 and Exhibits A and B which accompanied that response; see also Appeal Brief dated August 25, 2005 at pages 12-14 and Evidence Appendices 1 and 2 of the Appeal Brief

[17] See also *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002)

asserted that the intrinsic record in the present case supports the Examiner's interpretation of the term "library."[18]

Appellants disagree with both of these statements.

As noted above, the primary determinant of the meaning of a claim term is its ordinary and customary meaning to one of skill in the relevant art. The ordinary and customary meaning of "library," to a molecular biologist, is clear and Appellants have done nothing to alter or redefine that meaning.

Notwithstanding this fact, the intrinsic evidence is also consistent with the ordinary and customary meaning of the term "library" to a molecular biologist. As noted previously, a number of portions of the specification, including the examples, provide descriptions which make it clear that collections of different sequences are obtained by the practice of the claimed methods.[19]

Moreover, the Examiner has ignored certain intrinsic evidence in the present case, namely the intrinsic evidence of the prosecution history, which clearly shows that Appellants understand a library to comprise a collection of different molecules.[20] In this light it is noteworthy that, while the portion of *Bard v. U.S. Surgical* quoted in the Examiner's Reply states "[t]he intrinsic record includes the specification and the prosecution history;" in the sentence immediately following this quote, the Examiner states "[t]he Federal Circuit has clearly and consistently supported the position that the intrinsic evidence of the specification is determinative of the meaning of claims terms" (emphasis added).[21] Appellants submit that the Examiner has not properly considered all of the intrinsic evidence in construing the term "library" and, as a result, has improperly rejected the claims over Grosveld.

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[18] Examiner's Answer dated December 5, 2005 at pages 11-13

[19] See Response dated May 18, 2004 at pages 3-4 and Appeal Brief dated August 25, 2005 at page 10

[20] See Response dated May 18, 2004 at pages 2-3; Response dated June 16, 2004 at page 6 and Appeal Brief dated August 25, 2005 at pages 11-12

[21] Examiner's Answer dated December 5, 2005 at pages 11-12

(c) Limitations From the Preamble Should Be Read Into the Claims on Appeal

The Examiner states that the term "library," as used in the preamble, provides no structural limitation or manipulative difference to the claims.[22] Appellants assume that this argument applies only to claim 123 and its dependents, since independent claim 143 does not recite a "library" in the preamble. However, with respect to the cited art, Appellants submit that the use of "library" in the preamble of claim 123 should be read into the claims in the case on appeal, inasmuch as it makes it clear that the product of the method of claim 123 is a library (*i.e.* a collection of different sequences) while the only product taught by Grosveld is a clone.

Even if limitations from the preamble are not read into the claims, it remains the case that the method steps of claims 123 differ from the hypothetical method extracted from Grosveld's disclosure (and presented by the Examiner as the basis of the rejection). In particular, claim 123 specifies that a collection of fragments is obtained by contacting a cell nucleus with a first enzyme (claim 123, step (b)), deproteinizing (claim 123, step (c)), and contacting the deproteinized DNA with a second enzyme (claim 123, step (d)). The resulting collection of fragments, produced by the action of the first and second enzymes, is cloned (claim 123, step (e)).

By contrast, Grosveld teaches (at column 8) that, in one case, nuclei were treated with DNase I (first enzyme), then deproteinized DNA was recut with *Asp*718 or *Bgl*II (second enzymes).[23] In a second case, nuclei were treated with DNase I (first enzyme), and deproteinized DNA was recut with *Bam*HI (second enzyme).[24] However, in the portions of Grosveld selected from column 15, the DNA fragments that are cloned are an *Xba*I-*Xba*I fragment (containing DNaseI HS1), a *Hind*III-*Hind*III fragment (containing DNaseI HS2), a *Asp*718-*Sal*I fragment rendered blunt-ended (containing DNaseI HS3) and a partial *Sac*I fragment (containing DNaseI

[22] Examiner's Answer dated December 5, 2005 at pages 14-15

[23] U.S. Patent No. 5,635,355 at column 8, lines 17-32

[24] U.S. Patent No. 5,635,355 at column 8, lines 34-41

HS4).[25] Notably, none of these fragments which were cloned by Grosveld correspond to a DNaseI-*Asp*718 fragment, a DNaseI-*Bgl*II fragment or a DNaseI-*Bam*HI fragment, as described in column 8 of Grosveld.

Thus, the portions of Grosveld cited by the Examiner do not teach the cloning of a collection of fragments that have been produced by contacting nuclei with a first enzyme, deproteinizing and contacting the deproteinized DNA with a second enzyme, as claimed.[26]

(d) Grosveld Contains No Suggestion of Libraries As Claimed

The Examiner argues that, whether or not Grosveld teaches or suggests libraries, he nevertheless teaches the manipulative steps of the claims.[27] However, as shown in the previous section, Grosveld fails to teach the manipulative steps recited in the claims.

Furthermore, in response to Appellants' assertion that Grosveld fails to teach the preparation of libraries, the Examiner replied that Grosveld "at least has some suggestion of libraries."[28] The Examiner also stated that, even if the problem to be solved by Grosveld is different, or Grosveld's motivation is different, the fact that he suggests performing the manipulative steps of the invention renders the invention *prima facie* obvious.[29]

However, as noted repeatedly in the record and above, and despite any fleeting reference to libraries, Grosveld, in fact, fails to suggest the manipulative steps recited in the claims.

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[25] U.S. Patent No. 5,635,355 at column 15, lines 16-31

[26] Similarly, Grosveld fails to teach the steps of claim 143, inasmuch as he fails to disclose cloning of polynucleotides resulting from reaction of a probe with cellular chromatin followed by fragmentation of the probe-reacted chromatin

[27] Examiner's Answer dated December 5, 2005 at page 15

[28] Examiner's Answer dated December 5, 2005 at page 15

[29] Examiner's Answer dated December 5, 2005 at page 15

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the pending claims are patentable over the art cited by the Examiner. Accordingly, Appellant requests that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: February 2, 2006

By: 

Dahna S. Pasternak
Registration No. 41,411
Attorney for Appellant

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

CLAIMS ON APPEAL

1 to 122. (canceled).

123. (previously presented): A method for preparing a library of regulatory DNA sequences from a cell, the method comprising:

(a) providing a cell nucleus, wherein the nucleus comprises cellular chromatin;

(b) contacting the nucleus with a first enzyme, wherein the first enzyme reacts with accessible regions of cellular chromatin;

(c) deproteinizing the cellular chromatin to generate deproteinized DNA;

(d) contacting the deproteinized DNA with a second enzyme to generate DNA fragments;

(e) contacting the DNA fragments obtained in step (d) with a population of vector molecules, wherein the vector molecules comprise a first end that is compatible with the first enzyme and a second end that is compatible with the second enzyme, under conditions favorable to ligation of compatible ends; and

(f) selecting polynucleotides comprising a DNA fragment ligated to a vector molecule.

124. (previously presented): The method of claim 123, wherein the cell is selected from the group consisting of animal cells, plant cells and microbial cells.

125. (previously presented): The method of claim 123, wherein the first enzyme is a nuclease.

126. (previously presented): The method of claim 125, wherein the nuclease is DNase I.

127. (previously presented): The method of claim 125, wherein the nuclease is a restriction enzyme.

128. (previously presented): The method of claim 123, wherein the second enzyme is a restriction enzyme.

129. (previously presented): The method of claim 128, wherein the restriction enzyme is Sau3A I.

130. (previously presented): The method of claim 129, wherein the second end of the vector molecule is generated by digestion with BamH I.

131. (previously presented): The method of claim 126, wherein, subsequent to step (b), the DNase I ends are converted to blunt ends.

132. (previously presented): The method of claim 131, wherein the first end of the vector molecule is a blunt end.

133. (previously presented): The method of claim 132, wherein the first end of the vector molecule is generated by digestion with EcoRV or SmaI.

134. (previously presented): The method of claim 123 wherein, during steps (b) – (d), the nucleus is embedded in agarose.

135. (previously presented): The method of claim 123, wherein a plurality of different libraries of regulatory DNA sequences are prepared, wherein each library is obtained from a different cell.

136. (previously presented): The method of claim 135 wherein, in step (a), nuclei are obtained from cells at different stages of development.

137. (previously presented): The method of claim 135 wherein, in step (a), nuclei are obtained from cells in different tissues.

138. (previously presented): The method of claim 135 wherein, in step (a), nuclei are obtained from diseased cells and counterpart normal cells.

139. (previously presented): The method of claim 135 wherein, in step (a), nuclei are obtained from infected cells and counterpart uninfected cells.

140. (previously presented): The method of claim 135 wherein, in step (a), nuclei are obtained from cells that express a gene of interest at different levels.

141. (previously presented): The method of claim 123, wherein a plurality of different libraries of regulatory DNA sequences are prepared and, for each library, a different first enzyme is used.

142. (previously presented): The method of claim 141, wherein the different libraries are combined.

143. (previously presented): A method for isolating a collection of polynucleotides comprising cellular regulatory sequences, wherein the method comprises:

(a) contacting cellular chromatin with a probe, wherein the probe reacts with accessible regions of cellular chromatin;

(b) subsequently fragmenting the cellular chromatin to generate a collection of polynucleotide fragments; and

(c) selectively cloning polynucleotide fragments of step (b) comprising a site of probe reaction.

144. (previously presented): The method of claim 143, wherein reaction of the probe with cellular chromatin results in polynucleotide cleavage at the site of reaction.

145. (previously presented): The method of claim 143, wherein the cellular chromatin in present in an isolated nucleus.

146. (previously presented): The method of claim 145 wherein, in steps (a) and (b), the isolated nucleus is embedded in agarose.

147. (previously presented): The method of claim 143, wherein the probe is an enzyme.

148. (previously presented): The method of claim 147, wherein the enzyme is a nuclease.

149. (previously presented): The method of claim 148, wherein the nuclease is a restriction enzyme.

150. (previously presented): The method of claim 148, wherein the nuclease is DNase I.

151. (previously presented): The method of claim 143 wherein, in step (b), cellular chromatin is fragmented by restriction enzyme digestion.

152. (previously presented): The method of claim 151, wherein the restriction enzyme is Sau3A1.